UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,745	08/22/2005	Colin Maurice Casimir	20050022.ORI	3261

23595 7590 09/05/2006

NIKOLAI & MERSEREAU, P.A.
900 SECOND AVENUE SOUTH
SUITE 820
MINNEAPOLIS, MN 55402

EXAMINER	
SHEN, WU CHENG WINSTON	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/520,745	CASIMIR, COLIN MAURICE	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-67* is/are pending in the application.

4a) Of the above claim(s) *49 and 57-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-48 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application 10/520,745 filed on Aug. 22, 2005 is a 371 of PCT/GB03/03012 filed on 07/11/2003.

Election/Restriction

1. In response to the Restriction Requirement mailed on May 4, 2006, applicants elected the claims of Group I, claims 43-46, 48, 50-53, and 56, drawn to a viral particle having a modified cell binding activity and a method of making said viral particle comprising the recited steps.

Claims 47, 54, and 55 were not assigned to any of the groups in the Restriction Requirement mailed on May 4, 2006. Amendments of the three claims, 47, 54, and 55, are acknowledged and assigned to Group I as elected invention.

Applicant's election with traverse of Group I in the reply filed on June 05, 2006 is acknowledged. The traversal is based on the ground(s) that the novel linking feature of these groups is the way in which the binding specificity of the virus is modified and the consequences of that for targeted gene delivery. This is not found persuasive because inventions of Groups II-IV contain unique steps (Group II) or different processes of using the product (viral particle) (Groups III and IV), which are stated in the Restriction Requirement from last paragraph on page 3 to the end of second paragraph on page 4. Therefore, the inventions in Group I are patentably distinct from the inventions in Groups II-IV.

Accordingly, claim 49 (Group III), and claims 57-67 (Groups II and IV) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Status of claims: Claims 43-67 are pending. Claims 43-48 and 50-56 are currently under examination.

Information Disclosure Statement

The citation of GenBank Accession Number NM 002545 is crossed out due to lack of publication date.

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 43 and its dependent claims 44-48, 50-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, Pages 1099-111 (also available at www.uspto.gov).

When the claims are analyzed in light of the specification, instant invention encompasses any viral particle with any peptide binding moiety, either fused to the viral envelope protein or a separate peptide of the viral envelope protein, on the surface of the viral particle after budding from a packaging cell line, wherein the said viral packaging cell line comprises additional nucleic acid which can be expressed to provide any bioactive agent which is active in or on a target cell, and the said peptide binding moiety binds to any interacting binding moiety of the said peptide binding moiety, wherein the said interacting binding moiety is present on the plasma membrane of the cells specifically targeted by said viral particle. However, the specification discloses only (1) a specific passenger peptide binding moiety (See as defined on page 8), membrane bound stem cell factor (mb-SCF, Figure 2, examples 1-4, pages 49-70) that is a ligand and binds to the c-kit receptor protein found on the surface of quiescent stem cells (See 5th paragraph on page 14); (2) a specific Phoenix retroviral packaging cell line which is based on 293T cell line, a human embryonic kidney cell line, producing gag-pol genes with hygromycin as a co-selectable marker, and envelops proteins (either ectropic or amphotropic) with dipheria toxin as a second selectable marker (page 58, third paragraph); (3) a specific bioactive agent, β-galactosidase (page 10, last paragraph); and (4) a specific retroviral targeting cell line, human megakaryoblastic leukaemia cell line, Mo7e, for functional analysis of the binding of the mb-SCF viral particles to c-kit receptor positive cells (example 4, pages 67-70).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure/function information. In the instant case, the breadth of the invention encompasses any passenger peptide moiety expressed on any packaging cell line to be

incorporated into any viral particle that would targets to any cells bearing interacting structures of the said passenger peptide moiety. The mb-SCF (a passenger peptide moiety), the β-galactosidase (a bioactive agent), a Phoenix retroviral packaging cell line (a packaging cell line), a retroviral particle (a viral particle), and a c-kit receptor positive cells line, human megakaryoblastic leukaemia cell line, Mo7e (a targeted cell line), are the only species whose complete structure/function information is disclosed. The specification does not provide any disclosure as to what would have been the potential passenger peptide moiety, packaging cell line, viral particle, and targeted cell line encompassed by the breadth of the instant application.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than a passenger binding peptide moiety, a packaging cell line, a viral particle, and a targeted cell line), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is the mb-SCF present on the surface of a retroviral particle budding from a Phoenix retroviral packaging cell line, wherein β-galactosidase is expressed as a bioactive agent, and the said retroviral particle targets to a c-kit+ human megakaryoblastic leukaemia cell line. With regard to other passenger binding peptide moieties (claim 46) present on the surface of other viral particles budding from other packaging cell lines, wherein other bioactive agents (claims 51 and 52-53) are expressed, and the said passenger binding peptide moieties target to other cells (claim 55) than the mb-SCF present on the surface of other viral particle budding from other packaging cell line, wherein other bioactive agent than β-galactosidase is expressed as a bioactive agent, and the said viral particle targets to

other cell line, the specification does not provide any disclosure whether these other species would have had the same characteristics would have had additional characteristics or properties.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of besides the mb-SCF present on the surface of a retroviral particle budding from a Phoenix retroviral packaging cell line, wherein β-galactosidase is expressed as a bioactive agent, and the said retroviral particle targets to a c-kit+ human megakaryoblastic leukaemia cell line, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

4. Claims 43-48 and 50-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a retroviral particle, comprising providing a Phoenix retroviral packaging cell that produces gag-pol genes with hygromycin as a

co-selectable marker, and envelope protein (either ecotropic or amphotropic) with diphtheria toxin as a second selectable marker, and nucleic acid sequences encoding Epstein Barr Virus (EBV) Origin of Replication (oriP) and Epstein Barr Nuclear Antigen-1 (EBNA-1) gene enabling the plasmid to replicate as an episome, and transfecting the said retroviral packaging cell line with an expression vector comprising a nucleic acid encoding membrane bound human stem cell factor (SCF) operably linked to a eukaryotic promoter, wherein the said retroviral particle bearing SCF on the surface of the retroviral particle targeting to the c-kit+ megakaryoblastic leukaemia cell line, Mo7e, does not reasonably provide enablement for any non-retroviral particle having any peptide binding moiety on the viral surface, wherein the said peptide binding moiety is a passenger peptide binding moiety that is encoded and expressed by any viral packaging cell line and incorporated onto the surface of the said viral particle as a membrane bound protein during budding of the viral particles, wherein the said viral particles target to any cells by any types of interactions between the peptide binding moiety on the surface of the viral particle and any interacting binding partner on the plasma membrane of the cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention: The nature of the instant invention is a viral particle having a modified cell binding activity, and a method of making the said viral particle with modified cell binding activity comprising a viral particle that incorporates a passenger peptide binding moiety expressed on the plasma membrane of a viral packaging cell line during the maturation of the viral particle by budding.

The breadth of the claims: The breadth of the claims in the instant application encompasses any viral particle having any peptide binding moiety on the viral surface, wherein the said peptide binding moiety is a passenger peptide binding moiety that is encoded and expressed by any viral packaging cell line and incorporated onto the surface of the said viral particle as a membrane protein during budding of the viral particles, wherein the said viral

particles target to any cells by any types of interactions between the membrane bound peptide binding moiety on the surface of the viral particle and any interacting binding partner on the plasma membrane of the cells.

It is noted that, in the specification, applicant states, "By passenger peptide binding moiety, we mean a peptide with a binding moiety expressed by a viral packaging cell that is incorporated into viral particle during viral budding from a cell membrane". Accordingly, the breadth of "a viral packaging cell" encompasses any packaging cell line that can expresses any peptide binding moiety, including as a fusion protein, which comprises any different viral proteins and cellular receptors.

The state of the prior art and the relative skill of those in the art: Manel et al. reviewed the HTLV-1 tropism and envelope receptor stated, "The final step of virion release from retrovirus-infected consists of the coating of viral cores that contain the viral-encoded enzymes and dimeric RNA viral genome surrounded by capsid proteins. This step occurs through budding and egress of viral particles at the cell surface and provides virions with an envelope that is constituted by a plasma membrane-derived lipid bilayer enriched in viral envelope glycoproteins (Env)" (See page 6016, left column, first paragraph, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 2005 24(39): 6016-25, 2005).

Cronin et al., reviewed the altering the tropism of lentiviral vectors through pseudotyping stated, " One mechanism for expanding the cellular tropism of enveloped viruses is through the formation of phenotypically mixed particles or pseudotype, a process that commonly occurs during viral assembly in cells infected with two or more virus (See page 387, first paragraph,

Cronin et al., Altering the tropism of lentiviral vectors through pseudotyping. *Curr Gene Ther.* 5(4): 387-98, 2005).

Clapham et al., reviewed the complexity of interactions between HIV-1 receptor/co-receptor and HIV viral envelope protein, gp120, stated, "Variants that switch to use CXCR4 and perhaps other co-receptors evolve in some infected individuals and have altered tropism and pathogenic properties. Other cell surface receptors including mannose binding protein on macrophages and DC-SIGH on dendritic cells also interact with gp120 on virus particles but do not actively promoter fusion and virus entry (See abstract, Clapham et al., HIV-1 receptors and cell tropism. *Br Med Bull.* 58: 43-59, 2001).

Bittner et al, reported "CD4-D4-CXCR4 hybrids are useful for the generation of retroviral and lentiviral vectors with specificity for HIV-1 envelop expressing cells (See abstract, Bittner et al., Specific transduction of HIV-1 envelope expressing cells by retroviral vectors pseudotyped with hybrid CD4/CXCR4 receptors. *J Virol Methods.* 104(1): 83-92, 2002, listed on the IDS).

Jiang et al., reported "retroviral vectors displaying these scAs (single-chain antibodies) are component for infection in human cells which expresses the antigen recognized by the scA". (See abstract, Jiang et al, Cell-type-specific gene transfer into human cells with retroviral vectors that display single-chain antibodies. *J Virol.* 72(12): 10148-56, 1998, listed in IDS)

The predictability or lack thereof in the art: How a virus infects its host cell is determined by many factors including the interactions between viral envelope proteins and

receptor/co-receptor proteins on cell surface. Manel et al. reviewed the HTLV-1 tropism and envelope receptor stated, " --- tropism depends on many parameters that are independent of Env-receptor interactions, ---" (page 6022, right column, three paragraph under Conclusions and perspectives, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 24(39): 6016-25, 2005). For instance, "contacts between viruses and cell also occur outside of the *bona fide* Env-receptor interactions that lead to productive viral replication" (page 6016, right column, second paragraph, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 2005 24(39): 6016-25, 2005).

With regard to the alteration of viral tropism, and the concentration and purification of lentiviral vector pseudotypes, Cronin stated, "One problem with the methods outlined above is that cell-derived components are concentrated along with the vector particles leading to potential immune and inflammation responses (See page 390, second paragraph, Cronin et al., Altering the tropism of lentiviral vectors through pseudotyping. *Curr Gene Ther.* 5(4): 387-98, 2005). This issue is of particularly relevant with respect to the incorporation of a cellular protein, a passenger peptide binding moiety, into a viral particle that is regarded as the novelty of the instant application. How a viral particle incorporates, by budding, a desired passenger peptide binding moiety, which is engineered to be expressed in a packaging cell line, could vary dependent on the peptide binding moiety of interest, the expression level of the peptide binding moiety of interest, and the particular viral particle and packaging cell line being considered.

The presence or absence of working example: The specification provides working example of cloning of the human membrane bound SCF (mb-SCF) cDNA (example 1, page 49-

57), expression of the mb-SCF cDNA in the Phoenix retroviral packaging cells (example 2, page 57-62, production of retroviruses from the engineered Phoenix cells (example 3, pages 62-67), functionality of the mb-SCF viral particles (example 4, pages 67-70), and the method for transduction of the retroviral particle with mb-SCF on its surface to haematopoietic cell lines (pages 71-72). However, the specification does not provide any specific guidance with regard to how the examples listed can be modified for any other packaging cell line, expressing any peptide binding moiety, for the incorporation of the peptide binding moiety of interest into any viral particle.

The amount of direction or guidance and the quantity of experimentation needed: As discussed in the proceeding section, the amount of direction and guidance disclosed in the specification is limited to retroviral particles. With regard to the peptide binding moiety, the specification of instant application provides direction and guidance of mb-SCF whereas prior arts provided direction and guidance of (1) antibody (Jiang et al, Cell-type-specific gene transfer into human cells with retroviral vectors that display single-chain antibodies. *J Virol.* 72(12): 10148-56, 1998), and (2) receptor/co-receptor (Bittner et al., Specific transduction of HIV-1 envelope expressing cells by retroviral vectors pseudotyped with hybrid CD4/CXCR4 receptors. *J Virol Methods.* 104(1): 83-92, 2002, listed on the IDS). No specific direction and guidance is given regarding how the methods used for expressing mb-SCF can be modified to express any peptide binding moiety in any packaging cell line, for instance, the size limitation for and control of expressing a given peptide binding moiety of interest in any viral packaging cell line would

require undue experimentation for an skilled person in the art to make and use the claimed invention.

The specification as filed fails to provide any specific guidance and/or working examples, regarding non-retroviral particles. The specification also fails to direct the skilled artisan to any teachings on the relationship between the control of the expression level of a passenger peptide binding moiety and its incorporation into viral particles, and how this relationship affects the infectivity the viral particles to specific target cells, which would allow one of skill in the art to make and use the claimed invention without undue experimentation. In view of the state of the art, the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to practice the breadth of the claimed invention.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 43-48 and 54- 56 are rejected under 35 U.S.C. 102(a) as being anticipated by Jiang et al. (Jiang et al, Cell-type-specific gene transfer into human cells with retroviral vectors that display single-chain antibodies. *J Virol.* 72(12): 10148-56, 1998).

With regard to a passenger peptide-binding moiety on the surface of a viral particle (claims 43-48, 50, and 54- 56), Jiang et al. teach single-chain antibodies (scAs), as part of a fusion protein with envelope, directed against a carcinoembryonic antigen (CEA)-cross-reacting cell surface protein (See abstract, Figures 1 and 2).

With regard to viral particles (claims 43-48, 50, and 54- 56), Jiang et al. teach retroviral vector particles, derived from spleen necrosis virus (SNV) (See abstract and Figure 1).

With regard to viral packaging cell line (claims 43-48, 50 and 54- 56), Jiang et al. teach DSH-cxl cells that are SNV-derived retroviral packaging cells, which contain the retroviral vector pCXL (See page 10149, right column, last paragraph).

With regard to target cells (claims 43-48, 50 and 54- 56), Jiang et al. teach human cells, COLO-320DM (Fig. 4), which expresses the antigens, including Her3neu (Figure 3) and CD34 (Fig. 6), recognized by the scA. It was found that "increasing amounts of the N2 antibody added to the cells before infection blocked infectivity of anti-Her2neu-displaying particle. About 90% inhibition of infection was observed when 4 X 10^5 COLO-320DM cells were pre-incubated with about 10 μl of Mab solution harvested from the N2 hybridization cell line (Fig. 4A). No inhibition of infection was observed when such cells were pre-incubated with similar amounts of a different anti-Her2neu antibody". (See page 10152, second paragraph).

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (Jiang et al, *J Virol.* 72(12): 10148-56, 1998) in view of Dropulic et al. (U.S. patent No. 6,114,141, issued Sep. 5, 2000).

With regard to a passenger peptide-binding moiety on the surface of a viral particle, Jiang et al. teach single-chain antibodies (scAs), as part of a fusion protein with envelope, directed against a carcinoembryonic antigen (CEA)-cross-reacting cell surface protein (See abstract, Figures 1 and 2).

With regard to viral particles, Jiang et al. teach retroviral vector particles, derived from spleen necrosis virus (SNV) (See abstract and Figure 1).

With regard to viral packaging cell line, Jiang et al. teach DSH-cxl cells that are SNV-derived retroviral packaging cells, which contain the retroviral vector pCXL (See page 10149, right column, last paragraph).

With regard to target cells, Jiang et al. teach human cells, COLO-320DM (Fig. 4), which expresses the antigens, including Her2neu (Figure 3) and CD34 (Fig. 6), recognized by the scA. It was found that "increasing amounts of the N2 antibody added to the cells before infection blocked infectivity of anti-Her2neu-displaying particle. About 90% inhibition of infection was observed when 4 X 10^5 COLO-320DM cells were pre-incubated with about 10 μl of Mab solution harvested from the N2 hybridization cell line (Fig. 4A). No inhibition of infection was observed when such cells were pre-incubated with similar amounts of a different anti-Her2neu antibody". (See page 10152, second paragraph).

However, Jiang et al., do not teach additional nucleic acid which can express any one of the bioactive agent selected from ricin, tumor necrosis factor, interleukin-2 (a cytokine), interferon-gamma, ribonuclease, deoxyribonuclease, pseudomonas exotoxin A and caspase.

With regard to claim 51, Dropulic et al. teach methods to express genes from viral vectors (See title and abstract). Specifically, Dropulic et al. teach the expression of antiviral agent including a cytokine, a single-chain antibody, a cellular antigen or receptor (See claims 4 and 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the retroviral vector for the expression of single-chain antibodies by the teachings of Jiang et al. to express a cytokine (interleukine-2) as taught by Dropulic et al.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Jiang et al. to express antivial agent interleukin-2 by the teachings of Dropulic et al. to achieve the goal of site specific delivery of interleukin as an antiviral agent via the binding specificity of single-chain antibody.

There would have been a reasonable expectation of success given (1) the expression of single-chain Her2neu and CD34 antibodies targeted directly against the human cells surface antigens Her2neu and CD34 respectively by the teachings of Jiang et al., and (2) the expression of a cytokine from a viral vector by the teachings of Dropulic et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claims 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (Jiang et al, *J Virol.* 72(12): 10148-56, 1998) in view of Guber et al. (U.S. patent No. 569,177, issued Nov. 25, 1997).

With regard to a passenger peptide-binding moiety on the surface of a viral particle, Jiang et al. teach single-chain antibodies (scAs), as part of a fusion protein with envelope, directed against a carcinoembryonic antigen (CEA)-cross-reacting cell surface protein (See abstract, Figures 1 and 2).

With regard to viral particles, Jiang et al. teach retroviral vector particles, derived from spleen necrosis virus (SNV) (See abstract and Figure 1).

With regard to viral packaging cell line, Jiang et al. teach DSH-cxl cells that are SNV-derived retroviral packaging cells, which contain the retroviral vector pCXL (See page 10149, right column, last paragraph).

With regard to target cells, Jiang et al. teach human cells, COLO-320DM (Fig. 4), which expresses the antigens, including Her2neu (Figure 3) and CD34 (Fig. 6), recognized by the scA. It was found that "increasing amounts of the N2 antibody added to the cells before infection blocked infectivity of anti-Her2neu-displaying particle. About 90% inhibition of infection was observed when 4 X 10^5 COLO-320DM cells were pre-incubated with about 10 μl of Mab solution harvested from the N2 hybridization cell line (Fig. 4A). No inhibition of infection was observed when such cells were pre-incubated with similar amounts of a different anti-Her2neu antibody". (See page 10152, second paragraph).

However, Jiang et al., do not teach additional nucleic acid which can express any one of the bioactive agent, which is an enzyme, including thymidine kinase and cytosine deaminase, capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

With regard to claims 52-53, Guber et al. teach recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent (See title and abstract). Specifically, Guber et al. teach the expression of a nucleoside kinase thymidine kinase (See claims 6-8, 22-23) that converts a purine-based or pyridimine-based drug with little or no cytotoxicity into a cytotoxic drug (See claim 5)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the retroviral vector for the expression of single-chain antibodies by the teachings of Jiang et al. to express a thymidine kinase that converts a pro-drug into a cytotoxic drug as taught by Guber et al.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Jiang et al. to express thymidine kinase by the teachings of Guber et al. to achieve the goal of site specific delivery of interleukin as an antiviral agent converting a pro-drug into a cytotoxic drug via the binding specificity of single-chain antibody.

There would have been a reasonable expectation of success given (1) the expression of single-chain Her2neu and CD34 antibodies targeted directly against the human cells surface antigens Her2neu and CD34 respectively by the teachings of Jiang et al., and (2) the expression of thymidine kinase converting a pro-drug into a cytotoxic drug from a recombinant retroviral vector by the teachings of Guber et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Ram Shukla, can be reached on (571) 272-0735. The fax number for TC 1600 is (571) 273-8300. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Wu-Cheng Winston Shen

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER